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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/647,071	08/22/2003	Philip A. Swain	11662-003-999	9609

20583 7590 04/27/2010

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EXAMINER
STEELE, AMBER D

ART UNIT	PAPER NUMBER
1639	

MAIL DATE	DELIVERY MODE
04/27/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/647,071	SWAIN ET AL.	
	Examiner	Art Unit	
	AMBER D. STEELE	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/23/09,11/24/09,1/20/10,3/9/10*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *169-175* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *169-175* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/26/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 23 and 24, 2009 has been entered.

Status of the Claims

2. Claims 1-99, 105-108, and 110 were canceled, claims 101-103 and 109 were amended, and new claims 111-124 were added in the amendment to the claims received on June 1, 2006.

The amendment to the claims received on February 16, 2007 amended claims 100-101, 118; canceled claims 102, 114-116; and added new claims 125-140.

The amendment to the claims received on October 9, 2007 canceled claims 100-101, 103-104, 109, 111-113, 117-124, 127, and 130 and amended claims 125 and 129.

The amendment to the claims received on June 12, 2008 amended claim 125, canceled claims 129 and 139-140, and added new claims 141-142.

The amendment to the claims received on January 26, 2009 amended claims 125-126, 128, 131-138, and 142 and canceled claim 141.

The amendment to the claims received on June 11, 2009 amended claims 125 and 142.

The amendment received on August 26, 2009 amended claims 125 and 126 and canceled claims 143-160.

The amendment to the claims received on November 23 and 24, 2009 canceled all prior claims and added new claims 161-168.

The amendment to the claims received on January 20, 2010 canceled claims 161-168 and added new claims 169-175.

Claims 169-175 are currently pending and under consideration.

Election/Restrictions

3. The restriction requirement mailed on March 3, 2010 is withdrawn.

Priority

4. The present application claims status as a CON of 10/115,580 filed April 1, 2002 which is a CON of 09/882,803 filed June 14, 2001 which is a CON of 09/257,821 filed February 25, 1999 which is a CON of 08/720,487 filed September 30, 1996 (now U.S. Patent 5,876,727) which is a CIP of 08/563,673 filed November 28, 1995 (now U.S. Patent 5,760,184) which is a CIP of 08/414,971 filed March 31, 1995.

5. The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application Nos. 10/115,580; 09/882,803; 09/257,821; 08/720,487; 08/563,673; and 08/414,971, fails to provide adequate support or

enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The prior-filed applications do not provide support for the subgenus/species of a nicotine-*Pseudomonas* exotoxin pharmaceutical composition. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996). Also see *In re Ruschig*, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967) and *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1328, 56 USPQ2d 1481, 1487 (Fed. Cir. 2000). A "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species. Therefore, the presently filed application has a priority date of August 22, 2003.

Withdrawn Rejections

6. The rejection of claims 126, 148, 152, 156, and 160 under 35 U.S.C. 112, second paragraph is withdrawn in view of the cancellation of the claims.

7. The rejection of claims 145, 149, 153, and 157 under 35 U.S.C. 112, second paragraph is withdrawn in view of the cancellation of the claims.

8. The rejection of claims 125-126, 128, 131-138, and 142-160 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 5,876,727 alone or in combination with Green et al. U.S. Patent 5,601,831 is withdrawn in view of the cancellation of the claims.

9. The rejection of claims 125-126, 128, 131-138, and 142-160 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 88, 90, 103, 106, 108-109, and 128-135 of copending Application No. 11/472,215 is withdrawn in view of the cancellation of the claims.

10. The rejection of claims 125-126, 128, 131-138, and 142-160 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 119-135 of copending Application No. 11/472,220 is withdrawn in view of the cancellation of the claims.

New Objections

Claim Objections

11. Claim 173 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). The following is suggested: "of any one of claims 169-172".

12. Claims 169-175 are objected to because of the following informalities: independent claims 169 and 170 read "wherein n is independently an integer equal to…". Since the claims only have a single "n" in the formula, "independently" is considered superfluous. Appropriate correction is required.

New Rejections

Claim Rejections - 35 USC § 112

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 169-175 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **new matter** rejection. Applicants state on page 5 of the response received on January 20, 2010 that paragraph 110 of the published application reads "n is an integer, preferably selected from about 3 to about 20" and Figures 2A, 3B, and 4 provide examples where n = 0, n = 1, and n = 2. After careful review of Figure 2A, the present examiner of record could not find any designation for n in the figure. Furthermore, Figure 2A states that "Q" of CJ 1 (see present independent claim 170) can be H, COOH, halogen, 2-nitro-4-sulfophenyl ester, N-oxysuccinimidyl ester, carrier protein, modified carrier protein, or CJ 1.2 (i.e. **NOT** CJ 11 as required by present claim 172) and "Q" of CJ 7.1 (see present independent claim 169) can be halogen, COOH, carrier protein, or modified carrier protein (i.e. **NOT** CJ 3 as required by present claim 173). Regarding Figure 3B, this figure refers to cocaine-carrier conjugates (see page 12, Brief Description of the Figures for Figure 3b), does not disclose CJ 1 (i.e. present independent claim 170) as a primary linker (see PS-2, PS-3, PS-4, PS-5, PS-6, and PS-9 of Figure 3A), and in the disclosure of CJ 7.1 as the primary linker (i.e. present independent claim 169) Figure 3B(3) discloses PS-24 which does not include CJ 3 (i.e. present claim 171). Regarding Figure 4, this figure refers to cocaine-carrier and cocaine derivative/metabolite/analog-carrier conjugates (see pages 12-13, Brief Description of the

Figures for Figure 4), does not disclose CJ 1 (i.e. present independent claim 170) as a primary linker, and does not disclose CJ 7.1 as the primary linker (i.e. present independent claim 169). Therefore, the subgenus/species of compositions presently claimed are considered new matter.

15. Claims 169-175 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **written description** rejection.

With regard to the written description requirement, the attention of the Applicant is directed to The Court of Appeals for the Federal Circuit which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.,* 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original) [The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)] (the case is referred to herein as "*Lilly*").

Additionally, it is noted that written description is legally distinct from enablement: "Although the two concepts are entwined, they are distinct and each is evaluated under separate legal criteria. The written description requirement, a question of fact, ensures that the inventor conveys to others that he or she had possession of the claimed invention; whereas, the

enablement requirement, a question of law, ensures that the inventor conveys to others how to make and use the claimed invention." See 1242 OG 169 (January 30, 2001) citing *University of California v. Eli Lilly & Co.*

Although directed to DNA compounds, this *Eli Lilly* holding would be deemed to be applicable to any compound or a generic of compounds; which requires a representative sample of compounds and/or a showing of sufficient identifying characteristics; to demonstrate possession of the compound or generic(s). In this regard, applicant is further referred to *University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997); "Guidelines for Examination of Patent Applications Under the 35 USC 112, first paragraph, 'Written Description' Requirement" published in 1242 OG 168-178 (January 30, 2001); and *Univ. Of Rochester v G. D. Searle and Co.* 249 F. Supp. 2d 216 (W.D.N.Y. 2003) affirmed by the CAFC on February 13, 2004 (03-1304) publication pending.

Additionally, *Lilly* sets forth a two part test for written description:

A description of a genus of cDNA's may be achieved by means of a recitation of: a representative number of cDNA's, defined by nucleotide sequence, falling within the scope of the genus OR of a recitation of structural features common to the members of the genus. See *Regents of the University of California v. Eli Lilly & Co.* 119 F.3d 1559 (Fed. Cir. 1997) at 1569.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> …To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d

1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

Additionally, Cf. University of Rochester v G.D. Searle & Co., Inc., Monsanto Company, Pharmacia Corporation, and Pfizer Inc., No. 03-1304, 2004 WL 260813 (Fed. Cir., Feb. 13, 2004) held that:

Regardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods.

In the present instance, the specification discloses only limited examples that are not representative of the claimed subgenus/species of a pharmaceutical composition comprising nicotine and pseudomonas exotoxin linked via CJ 7.1 alone or combined with CJ3 or CJ 1 alone or combined with CJ 11; nor do the claims recite sufficient structural feature(s) which is(are) common to members of the subgenus/species sufficient to demonstrate possession of the subgenus/species.

The Examiner further notes the present claims stated by Applicant are broader in scope that those that were held to be impermissible in *Lilly* because, unlike *Lilly*, Applicants' claims encompass a vast number of linkers (i.e. Q is another branch identified by CJ number) and pharmaceutically acceptable excipients. The scope of these claims include a vast number of components because the linkers and "pharmaceutically acceptable excipient" are not specifically defined in the specification. Furthermore, the specification and claims do not place any limit on

the number of components, the types of components, or the manner in which the components might be connected to form a pharmaceutical composition comprising nicotine and pseudomonas exotoxin. Therefore, Applicant is using an inadequately described linker and pharmaceutically acceptable excipient to describe the presently claimed pharmaceutical composition. Consequently, there is no teaching that would allow a person of skill in the art to determine *a priori* that the Applicant was in possession of the full scope of the claimed invention at the time of filing because there is no common structural attributes that can link together all of the claimed "pharmaceutical composition".

The general knowledge and level of skill in the art for the relationship between antigens and antibodies and utilization of adjuvants and carriers to enhance the immune response is high, the general knowledge and level of skill in the art for producing pharmaceutical compositions that are efficacious and safe in humans is low (i.e. few drugs reach phase IV clinical trials; references will be provided if requested by applicants). Therefore, the knowledge and level of skill does not supplement the omitted description because specific, not general, guidance is needed for the "pharmaceutical composition". Since the disclosure fails to describe the common attributes or characteristics that identify all of the members of the genus or even a substantial portion thereof, and because the genus is vast and highly variant (e.g. linkers and pharmaceutically acceptable excipient), the limited examples in the specification is insufficient to teach the entire subgenus.

The specification discloses only limited examples that are not representative of the claimed subgenus/species of a pharmaceutical composition comprising nicotine and pseudomonas exotoxin; nor do the claims recite sufficient structural feature(s) which is(are)

common to members of the subgenus/species sufficient to demonstrate possession of the subgenus/species. Therefore, the teachings in the specification are general teachings relating without guidance as to the individual components of the product. In addition, there are numerous linkers and pharmaceutically acceptable excipients that could be employed in the invention with little direction or guidance for one of skill in the art to make the claimed invention.

Furthermore, a lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996). Also see *In re Ruschig*, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967) and *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1328, 56 USPQ2d 1481, 1487 (Fed. Cir. 2000). A "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species. In the present specification, the laundry list of potential carriers, potential linkers, and potential pharmaceutically acceptable excipients would not reasonably lead one of skill in the art to the presently claimed subgenus/species particularly when the present specification focused on nicotine conjugated to BSA or CTB carriers (see Examples 26-30).

See pages 27-28 regarding laundry list of potential carriers: "Suitable carrier molecules are numerous and include, but are not limited to: Bacterial toxins or products , for example, cholera toxin B- 35 (CTB), diphtheria toxin, tetanus toxoid, and pertussis toxin and filamentous hemagglutinin, shiga toxin, pseudomonas exotoxin; Lectins, for example, ricin-B subunit, abrin and sweet pea lectin; Subvirals, for example, retrovirus nucleoprotein (retroNP), rabies ribonucleoprotein (rabies RNP), plant viruses (e.g. TMV, cow pea and cauliflower mosaic viruses), vesicular stomatitis virus-nucleocapsid protein (VSV-N), poxvirus vectors and Semliki forest virus vectors; Artificial vehicles, for example, multiantigenic peptides (MAP), microspheres; Yeast virus-like particles (VLPs); Malarial protein antigen; and others such as proteins and peptides as well as any modifications, derivatives or analogs of the above. To

determine features of suitable carriers, initial experiments were performed using bovine serum albumin as a protein carrier."

See pages 35-36 regarding the laundry list of potential linkers: CJ 0, 1, 1.1, 1.2, 2, 2.1, 2.2, 2.3, 3, 3.1, 4, 4.1, 5, 5.1, 6, 7, 7.1, 8, 8.1, 9, 10, and 11 "wherein n is an integer preferably selected from about 3 to about 20, more particularly about 3 to about 6; Y is preferably selected from the group consisting of S, O, and NH; and Q is preferably selected from the group consisting of: -H, -OH, -CH2, -CH3, -OCH3, -COOH, halogen, protein or peptide carrier, modified protein or peptide carrier, activated esters, such as 2-nitro-4-sulfophenyl ester and N-oxysuccinimidyl ester, groups reactive towards carriers or modified carriers such as mixed anhydrides, acyl halides, acyl azides, alkyl halides, N-maleimides, imino esters, isocyanate, isothiocyanate ; or another "branch" identified by its "CJ" reference number".

See pages 54-55 regarding the laundry list of potential pharmaceutically acceptable excipients: "Therapeutic compositions may optionally contain one or more pharmaceutically acceptable excipients including, but not limited to, sterile water, salt solutions such as saline, sodium phosphate, sodium chloride, alcohol, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycol, gelatine, mannitol, carbohydrates, magnesium stearate, viscous paraffin, fatty acid esters, hydroxy methyl cellulose, and buffer. Other suitable excipients may be used by those skilled in that art. The composition of the present invention may also contain further adjuvants, agents and/or inert pharmacologically acceptable excipients which may be added to enhance the therapeutic properties of the drug or enable alternative modes of administration."

The laundry list of potential carriers, linkers, and pharmaceutically acceptable excipients would result in at least thousands of different compositions without reasonably leading one of skill in the art to the presently claimed subgenus/species as claimed. The expedient statements in the specification do not relate to an adequate disclosure or how to make and use the claimed invention. Consequently, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to adequately describe the vast genus. Thus, Applicant does not appear to be in possession of the claimed genus.

16. Claims 169-175 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for a "hapten-carrier conjugate", the specification does not reasonably provide enablement for "a pharmaceutical composition". The specification does not

enable a person skilled in the art to make and use the invention commensurate in scope with the claim. This is a **scope of enablement** rejection.

There are many factors to consider when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any experimentation is "undue". These factors include, but are not limited to:

1. The breadth of the claims;
2. The nature of the invention;
3. The state of the prior art;
4. The level of skill in the art;
5. The level of predictability in the art;
6. The amount of direction provided by the inventor;
7. The presence or absence of working examples;
8. The quantity of experimentation necessary needed to make or use the invention based on the disclosure.

See *In re Wands* USPQ 2d 1400 (CAFC 1988):

The breadth of the claims and the nature of the invention:

Although requiring a specific carrier (i.e. pseudomonas exotoxin) and nicotine, the claims refer to a large subgenus of linkers (e.g. CJ 7.1 alone or in combination with CJ 3 or CJ 1 alone or in combination with CJ 11 wherein Q is any other branch identified by CJ number) and a large genus of pharmaceutically acceptable excipients. Accordingly, the claims encompass a vast number pharmaceutical compositions due to the variety of linkers and pharmaceutically acceptable excipients. Intended use as a "pharmaceutical composition" does not provide any

information regarding the required structure of the composition. Accordingly, the claim scope is unduly broad with respect to the encompassed compositions.

The state of the prior art and the level of predictability in the art:

Pharmaceutical compositions comprising nicotine conjugated to pseudomonas exotoxin is highly unpredictable in the art, particularly regarding the intended use as a pharmaceutical composition. Various issues may arise during pre-clinical or early clinical experimentation related to toxicity, efficacy, specificity for intended targets (i.e. nicotine), unacceptable side effects (e.g. risk/benefit analysis), delivery formulation (e.g. oral, intravenous, etc.), pharmacokinetics, pharmacodynamics, development of drug resistance, monotherapy verses combination therapy, etc. While there is a need in the art for successful preventative therapies for nicotine addiction, the state of the art requires vast amounts of data from both *in vitro* and *in vivo* experiments, utilizing *in vivo* animal models, *in vivo* experiments to determine efficacy, toxicity, etc. prior to clinical trials (e.g. Phase 0 studies) without guaranteed success in humans (e.g. Phases I-IV). For example, Kosten et al. (Pharmacology & Therapeutics 108: 76-85, 2005 and Vaccine 20: 1196-1204, 2002) teach various potential disadvantages to hapten-protein conjugate vaccination (i.e. active immunization) including requirement for multiple boosters since exposure to haptens does not induce antibody production (e.g. no secondary response); the carrier must be highly immunogenic in order to produce sufficient antibody levels; several factors can alter antibody serum levels including the quality of the vaccine, dose, frequency of boosters, time interval between boosters, etc.; patient compliance particularly in drug abusers; potential for allergic reactions to proteins conjugated to haptens due to high level of immunogenicity; ability to surmount the effects of vaccination via using higher doses of drug

(i.e. prevention difficult); 2-6 months required to produce sufficient antibody titers; etc. (please refer to entire reference, particularly page 78, right column; page 79, right column). In addition, Rose (2008, Ann. N.Y. Acad. Sci., 1141: 233-256) teaches that animal studies have shown antibody concentrations of 440 nM in response to nicotine vaccines (see the entire references particularly page 241). However, this amount of nicotine antibodies would only bind the dose of nicotine in less than five puffs of a typical cigarette. Therefore, the available antibody would quickly become saturated and nicotine inhaled from subsequent inhalation of cigarette smoke would bypass the saturated antibodies. Furthermore, nicotine vaccines might not relieve withdrawal symptoms. Cerny et al. (2008 Expert Opin. Investig. Drugs 17(5): 691-696) teach that of the three nicotine vaccines in clinical trials including *Pseudomonas aeruginosa* exopreotein A conjugated to 3'-aminomethylnicotine (i.e. Nabi Pharm.) require high dosages to obtain sufficient antibody responses and has a relatively high incidence of side effects (please refer to the entire reference particularly pages 693 and 695). Therefore, the level of predictability in the art is dependent on many factors including the specific formulation of the nicotine-carrier conjugate, dosage, multiple boosters provided at distinct intervals, patient compliance, etc. While treating addiction to nicotine is important, the state of the art requires vast amounts of data including Phase 0-IV trials.

The level of skill in the art:

The level of skill would be high, most likely at the Ph.D. level.

The amount of direction provided by the inventor and the existence of working examples:

There are no specific examples directed to the presently claimed invention of a nicotine linked to *Pseudomonas* exotoxin; nor is there any guidance as to how to specifically utilize a

pharmaceutical composition comprising nicotine linked to *Pseudomonas* exotoxin which is within the scope of the presently claimed invention.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure:

In light of the unpredictability surrounding the claimed subject matter, the undue breadth of the claimed invention's intended use, and the lack of adequate guidance, one wishing to practice the presently claimed invention would be unable to do so without engaging in undue experimentation. One wishing to practice the presently claimed invention would have to produce additional *in vitro* experiments utilizing animal models for preventing nicotine addiction to determine if the pharmacological and psychologically addictive effects of nicotine are altered and perform Phase I-IV clinical trials. In addition, *in vitro* and clinical trials for nicotine and *Pseudomonas* exotoxin compositions would be necessary (see present claim 125).

17. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. Claims 169-170 and 173-175 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. One of skill in the art would not be able to determine the scope of the presently claimed invention. For example, "Q is another branch identified by its CJ number" and "a pharmaceutically acceptable excipient" are not clearly defined in the present claims. What structure does Q have, what is included, and what is excluded? What are pharmaceutically acceptable excipients, what is included, and what is excluded?

Claim Rejections - 35 USC § 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20. Claims 169-174 are rejected under 35 U.S.C. 102(b) as being anticipated by Ennifar et al. U.S. Patent 6,232,082 issued May 15, 2001.

For present claims 169-174, Ennifar et al. teach nicotin-carrier conjugates wherein the carrier is *Pseudomonas* exoprotein A, various linkers and excipients, and alum adjuvants (please refer to the entire specification particularly the abstract; columns 3-8, 11-12, 14).

Therefore, the teachings of Ennifar et al. anticipate the presently claimed invention.

Claim Rejections - 35 USC § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. Claims 169-175 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walling et al. U.S. Patent 5,164,504 issued November 17, 1992; Swain et al. WO 98/14216 published April 9, 1998; Glenn et al. U.S. Patent 5,980,898 with an effective filing date of November 14, 1996; and Layton et al.., Factors influencing the immunogenicity of the haptenic drug chlorhexidine in mice, Immunology 59: 459-465, 1986.

For present claims 169-172, Walling et al. teach nicotine, cotinine, and cotinine derivative hapten-carrier conjugates wherein the hapten is cotinine, trans-3'-cotinine, or cotinine-N-oxide, the carrier can be various proteins or peptides, and the carrier is covalently bound to the hapten via direct linkage (i.e. CJ 0), $(CH_2)_2CONH$ (i.e. CJ 6 where n = 2), or as represented in Formula I (please refer to column 2) wherein X is a straight or branched chain, saturated or unsaturated, divalent radical which has from 1-10 carbon atoms and 1-2 hetero atoms selected from the group consisting of S, O, and NZ wherein Z is a C_1-C_3 alkyl group and Q is a functional group selected from –COOH, $-NH_2$, $-C(O)NHNH_2$, -O(CO)Cl, -CHO, -NCS, or –NCO (please refer to the entire specification particularly the abstract; Formulas I, IV, V, VI, , VII, VIII, IX, X, XI, XII, XV, and XVI; columns 1-8; Examples 1-8; claims 1-6; and Table 1). In addition, Walling et al. teach utilizing S, O, and NH molecules in the branches joining the hapten and the carrier (please refer to columns 2-6). Furthermore, Walling et al. teach utilizing the hapten-carrier conjugates as immugens and eliciting immune responses in various animals (please refer to column 6). MPEP § 2144.09 states the following: "homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by $-CH_2-$ groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977). See also *In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978). Walling et al. teach various excipients and "auxiliary agents" (i.e. pharmaceutically acceptable excipient; please refer to Examples 1-3 and 6-8).

For present claim 173, Walling et al. teach pristine (i.e. adjuvant; please refer to column 7, lines 24-31).

However, Walling et al. does not teach *Pseudomonas* exotoxin carriers.

For present claims 169-173, Glenn et al. teach a transcutaneous immunization system comprising antigen/hapten, adjuvant, and/or carriers (i.e. antigens, adjuvants, and carriers can be the same or different molecules) wherein the hapten/adjuvant/carrier is preferably ADP-ribosylating exotoxins including *Pseudomonas* exotoxin and the composition can also contain hydrating agents, penetration enhancers, pharmaceutically acceptable additives, diluents, binders, stabilizers, preservatives, colorings, buffers, liposomes, etc. (i.e. pharmaceutically acceptable excipient, auxiliary agent, and supplementary active compound; please refer to the entire specification particularly the abstract; columns 1, 3-5, and 6-10; and Examples columns 16-29).

However, neither Walling et al. nor Glenn et al. teach the specific adjuvant of alum or more specifically aluminum hydroxide.

For present claims 173-175, Layton et al. teach haptens, carriers, and adjuvants including alum and, specifically, aluminum hydroxide (please refer to the entire reference particularly the Summary, Introduction, and the Reagents section of the Materials and Methods).

However, Walling et al., Glenn et al., and Layton et al. do not teach the specific linkers.

For present claims 169-172, Swain et al. teach CJ 7.1, CJ 1, CJ 3, and CJ 11 linking nicotine to carriers (see the entire specification particularly pages 27-29).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the nicotine hapten-carrier conjugates taught by Walling et al. with the specific carrier (i.e. *Pseudomona*s exotoxin) taught by Glenn et al.

One having ordinary skill in the art would have been motivated to do this because Glenn et al. teach that *Pseudomonas* exotoxin elicits a strong immune response (please refer to column 1, lines 15-28; column 2, lines 39-67; column 3, lines 1-20; and Figures 1A-2D).

One of ordinary skill in the art would have had a reasonable expectation of success in the modification of the nicotine hapten-carrier conjugates taught by Walling et al. with the specific carrier (i.e. *Pseudomonas* exotoxin) taught by Glenn et al. because of the results obtained by Glenn et al. (please refer to Figures 1A-2D).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the nicotine hapten-bacterial toxin conjugates taught by Walling et al. and Glenn et al. with the alum adjuvant taught by Layton et al.

One having ordinary skill in the art would have been motivated to do this because Layton et al. teach that the carrier can be immunogenic and/or an adjuvant can be utilized to enhance the immune response of the hapten (please refer to the Introduction; page 461, The effects of adjuvants on the immunogenicity of chlorhexidine; Table 2; and Figures 2-5).

One of ordinary skill in the art would have had a reasonable expectation of success in the modification of the nicotine hapten-bacterial toxin conjugates taught by Walling et al. and Glenn et al. with the alum adjuvant taught by Layton et al. because of the results (i.e. immune response) provided by Layton et al. (please refer to Table 2 and Figures 2-5).

The claims would have been obvious because the substitution of one known element (i.e. linkers taught by Walling et al.) with linkers taught by (Swain et al.) would have yielded predictable results (i.e. linkage of nicotine to carrier) to one of ordinary skill in the art at the time of the invention. See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

Therefore, the modification of the nicotine derivative hapten-bacterial toxin conjugates taught by Walling et al. and Glenn et al. with the alum adjuvant taught by Layton et al. and the linkers taught by Swain et al. render the instant claims *prima facie* obvious.

23. Claims 169-175 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ennifar et al. U.S. Patent 6,232,082 issued May 15, 2001 and Layton et al.., Factors influencing the immunogenicity of the haptenic drug chlorhexidine in mice, Immunology 59: 459-465, 1986.

For present claims 169-174, Ennifar et al. teach nicotin-carrier conjugates wherein the carrier is *Pseudomonas* exoprotein A, various linkers and excipients, and alum adjuvants (please refer to the entire specification particularly the abstract; columns 3-8, 11-12, 14).

However, Ennifar et al. does not specifically teach aluminum hydroxide.

For present claims 173-175, Layton et al. teach haptens, carriers, and adjuvants including alum and, specifically, aluminum hydroxide (please refer to the entire reference particularly the Summary, Introduction, and the Reagents section of the Materials and Methods).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the nicotine hapten-carrier conjugates taught by Ennifar et al. with the aluminum hydroxide adjuvant taught by Layton et al.

One having ordinary skill in the art would have been motivated to do this because Layton et al. teach that the carrier can be immunogenic and/or an adjuvant can be utilized to enhance the immune response of the hapten (please refer to the Introduction; page 461, The effects of adjuvants on the immunogenicity of chlorhexidine; Table 2; and Figures 2-5).

One of ordinary skill in the art would have had a reasonable expectation of success in the modification of the nicotine hapten-carrier conjugates taught by Ennifar et al. with the aluminum hydroxide adjuvant taught by Layton et al. because of the results (i.e. immune response) provided by Layton et al. (please refer to Table 2 and Figures 2-5).

The claims would have been obvious because the substitution of one known element (i.e. alum adjuvant taught by Ennifar et al.) for another (i.e. the aluminum hydroxide adjuvant taught by Layton et al.) would have yielded predictable results (i.e. enhanced immune response) to one of ordinary skill in the art at the time of the invention. See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

Therefore, the modification of the nicotine hapten-carrier conjugates taught by Ennifar et al. with the alum adjuvant taught by Layton et al. and the linkers taught by Swain et al. render the instant claims *prima facie* obvious.

Double Patenting

24. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225

USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

25. Claims 169-175 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 4-5, 8-12, and 17-18 of U.S. Patent No. 5,876,727 in view of Glenn et al. U.S. Patent 5,980,898 with an effective filing date of November 14, 1996. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the presently claimed inventions and the inventions as claimed in U.S. Patent No. 5,876,727 claim nicotine haptens conjugated to a carrier and pharmaceutical compositions of the hapten-carrier.

For present claims 169-172, U.S. Patent No. 5,876,727 claims a nicotine hapten-carrier conjugate comprising the structure shown in Figures 17b and 18 (e.g. nicotine derivative hapten wherein chemical moieties may be at positions A-F and not simply utilized as a linker between

the hapten and the carrier) and side chains (e.g. branch) of CJ 0, 1, 1.1, 1.2, 1.3, 2, 2.1, 2.2, 2.3, 3, 3.1, 4, 4.1, 5, 5.1, 6, 7, 7.1, 8, 8.1, 9, 10, and 11 (where the CJ structures are claimed, n = an integer, and Q is a carrier) and a T-cell epitope carrier (please refer to claim 1). In addition, regarding pseudomonas exotoxin, Glenn et al. teach a transcutaneous immunization system comprising antigen/hapten, adjuvant, and/or carriers (i.e. antigens, adjuvants, and carriers can be the same or different molecules) wherein the hapten/adjuvant/carrier is preferably ADP-ribosylating exotoxins including *Pseudomonas* exotoxin and the composition can also contain hydrating agents, penetration enhancers, pharmaceutically acceptable additives, diluents, binders, stabilizers, preservatives, colorings, buffers, liposomes, etc. (i.e. pharmaceutically acceptable excipient, auxiliary agent, and supplementary active compound; please refer to the entire specification particularly the abstract; columns 1, 3-5, and 6-10; and Examples columns 16-29).

For present claims 169-173, U.S. Patent 5,876,727 claims a pharmaceutically acceptable carrier, an aqueous solution at a physiologically acceptable pH, and adjuvants (e.g. pharmaceutically acceptable excipient; please refer to claims 8-11).

For present claims 174-175, U.S. Patent 5,876,727 claims alum (i.e. aluminum hydroxide), MF59, or RIBI adjuvants (please refer to claims 9-10).

Therefore, the claims of U.S. Patent 5,876,727 render the presently claimed invention *prima facie* obvious.

26. Claims 169-175 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 88, 90, 103, 106, 108, 109, 128, 130, and 132-149 of copending Application No. 11/472,215 in view of Glenn et al. U.S. Patent

5,980,898 with an effective filing date of November 14, 1996. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the presently claimed inventions and the inventions claimed in U.S. Patent application 11/472,215 claim nicotine hapten-carrier conjugates and pharmaceutical compositions.

For present claims 169-175, U.S. application 11/472,215 claim a nicotine hapten-carrier conjugate comprising the structure shown in Fig. 17b (e.g. nicotine derivative hapten) and branches of CJ 0, 1, 1.1, 1.2, 1.3, 2, 2.1, 2.2, 2.3, 3, 3.1, 4, 4.1, 5, 5.1, 6, 7, 7.1, 8, 8.1, 9, 10, and 11 wherein Y (e.g. for the CJ structures) is S, O, or NH (where the CJ structures are claimed, n = an integer, and Q is a carrier) and a subviral carrier (please refer to claims 88 and 91). In addition, regarding pseudomonas exotoxin, Glenn et al. teach a transcutaneous immunization system comprising antigen/hapten, adjuvant, and/or carriers (i.e. antigens, adjuvants, and carriers can be the same or different molecules) wherein the hapten/adjuvant/carrier is preferably ADP-ribosylating exotoxins including *Pseudomonas* exotoxin and the composition can also contain hydrating agents, penetration enhancers, pharmaceutically acceptable additives, diluents, binders, stabilizers, preservatives, colorings, buffers, liposomes, etc. (i.e. pharmaceutically acceptable excipient, auxiliary agent, and supplementary active compound; please refer to the entire specification particularly the abstract; columns 1, 3-5, and 6-10; and Examples columns 16-29).

For present claims 173-175, U.S. application 11/472,215 claim alum including aluminum hydroxide or aluminum phosphate, MF59, or RIBI adjuvants (please refer to claims 106-108).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

27. The art including prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US Patents 6,932,971; 7,247,502; 6,773,891; 6,518,031; and 7,446,205.

Future Communications

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMBER D. STEELE whose telephone number is (571)272-5538. The examiner can normally be reached on Monday through Friday 9:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Amber D. Steele/
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